

Reconstructing the past: The First Ancient Human Genome

Course:

Bioinformatics for Human Biologists



First Ancient Human Genome



The Saqqaq Genome

4,000 years

Hair sample from permafrost

DNA extraction <10% contamination

20 x coverage

Started 2009



Eske Willerslev

The Neandertal Genome

38,000 years

Leg bone from a cave in Croatia

DNA extraction >95% contamination

1 x coverage

Started 2006



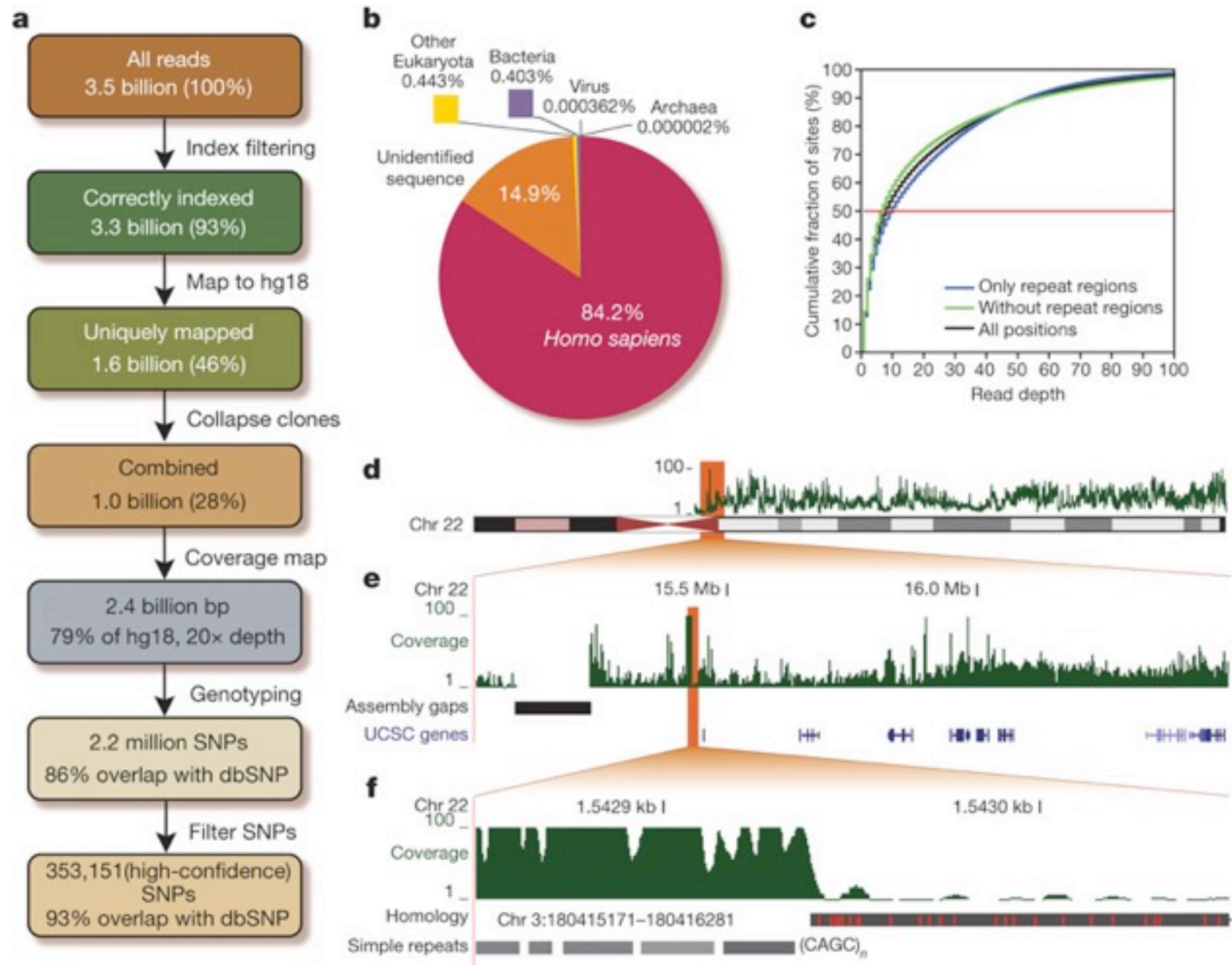
DNA from hair



DNA from hair

- Hardly any contamination
- Relatively high yield
- Short fragments
- <3 month sequencing
- Post-mortem DNA damage
- Phusion Polymerase

Flow chart over pipeline and data summary

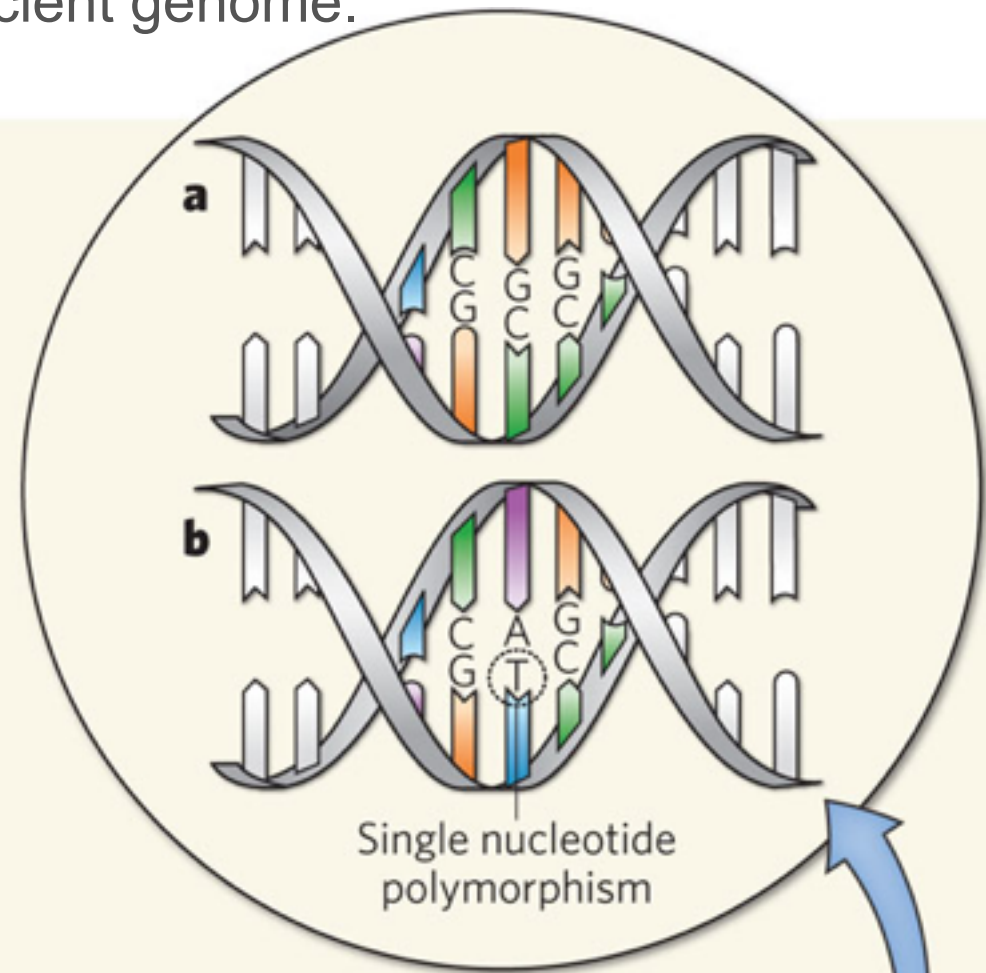


Functional SNP assessment

What can we say about his phenotype?

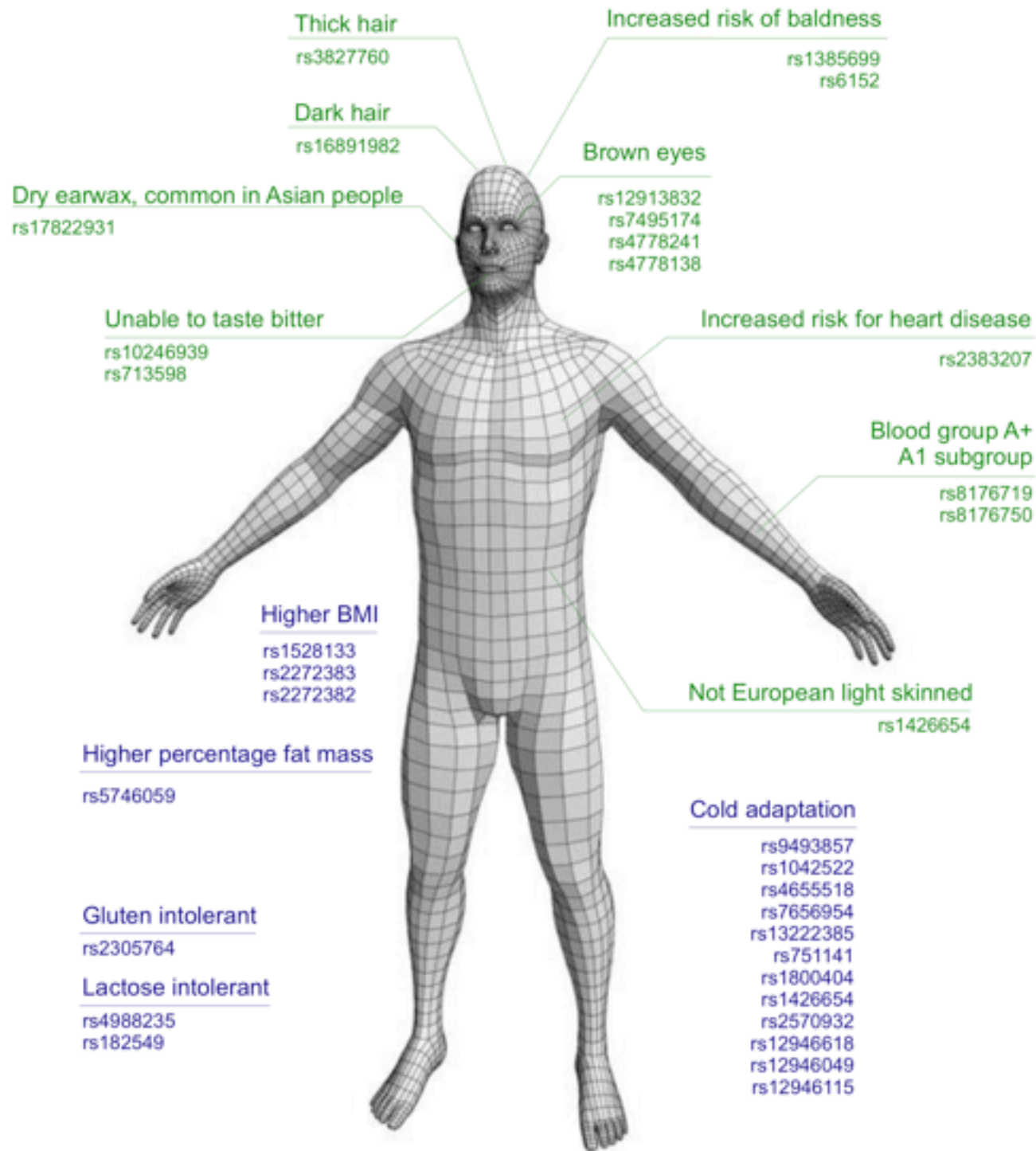
Single nucleotide polymorphisms of an ancient genome.

Rasmussen *et al.*² have sequenced the genome of a man from the Saqqaq culture, using DNA from hair preserved in permafrost in Greenland. They analysed the genome to find single nucleotide polymorphisms (SNPs) — differences in single DNA base pairs that exist between individual genomes, and that may act as markers of an individual's physical traits. **a**, Here, a short stretch of human DNA is shown that is a marker for normal earwax. **b**, In the analogous DNA from the Saqqaq individual, there is a SNP in which a C in the lower strand has been replaced by a T (C, G, T and A denote the four kinds of DNA base). This SNP shows that the Saqqaq man had dry earwax. Rasmussen and colleagues identified other SNPs indicating that the ancient human had, among other things, brown eyes, non-white skin, thick dark hair and an increased susceptibility to baldness.



From the following article:
Evolutionary biology: Face of the past reconstructed
David M. Lambert & Leon Huynen
Nature **463**, 739-740(11 February 2010)
doi:10.1038/463739a





Population genetics and phylogenetics

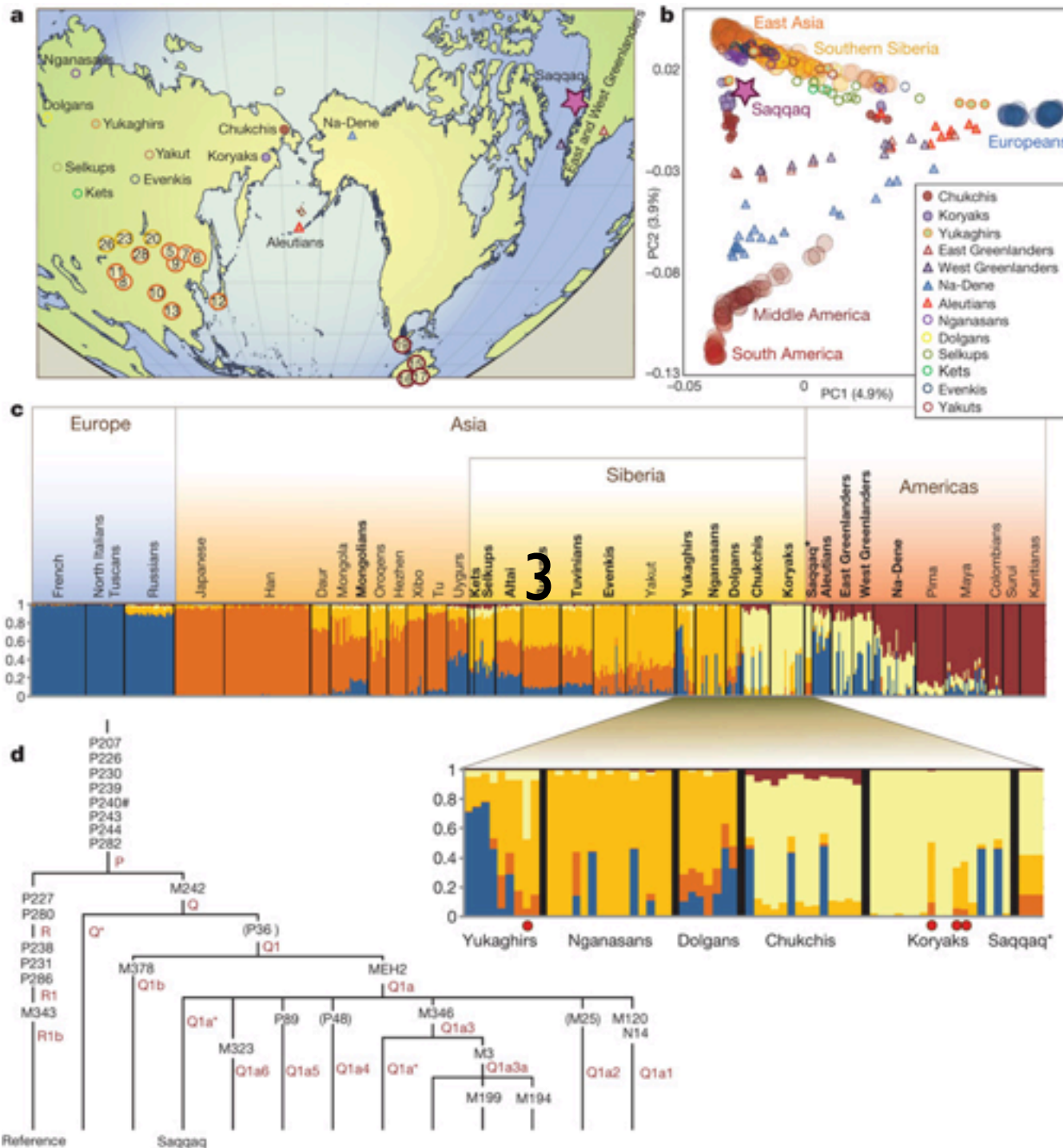








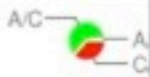



















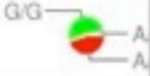









Table S14. List of SNP identifiers used for functional assessment. Associations to phenotype were curated from literature, public databases and HGMD Professional. Frequencies from Hapmap Phase-II are represented in pie charts, with the colour of the Saqqaq Allele matching the corresponding genotype in the pie charts. In most cases, the Saqqaq allele is closest to the Asian (Han Chinese and Japanese) populations.

SNP	Reference	1-pp	Saqqaq Allele	HapMap frequencies			
				CEU	HCB	JPT	YRI
rs8176719 ¹	66	NA	-/-	NA	NA	NA	NA
rs8176750 ²	67	8.84E-34	G/G	NA	NA	NA	NA
rs12913832 ³	68	5.13E-10	A/A				
rs7495174 ³	68	1.14E-25	A/G				
rs4778241 ³	68	8.24E-06	A/A				
rs1129038 ³	68	8.69E-40	C/C	NA	NA	NA	NA
rs1426654 ⁴	69	8.78E-12	G/G				
rs1385699 ⁵	70	8.57E-05	T/T				
rs6152 ⁵	71	4.12E-21	G/G	NA	NA	NA	NA
rs1528133 ⁶	63	1.50E-08	A/C				
rs2272383 ⁶	63	1.42E-27	A/G				
rs2272382 ⁶	63	8.40E-60	A/G				
rs5746059 ⁷	62	1.64E-05	A/A				

rs17822931 ⁸	72	8.36E-09	T/T				
rs3827760 ⁹	73	5.61E-12	C/C				
rs16891982 ¹⁰	74	3.87E-13	C/C				
rs1042522 ¹¹	75	2.75E-11	G/G				
rs13222385 ¹²	59	3.21E-05	A/G				
rs751141 ¹²	59	2.13E-07	T/T				
rs1800404 ¹²	59	2.51E-14	A/A				
rs1426654 ¹²	59	8.78E-12	G/G				
rs2570932 ¹²	59	0.001509 7	C/C				
rs12946618 ¹²	59	0.001380 2	A/A				
rs12946115 ¹²	59	2.44E-06	C/C				

¹Blood Group: not type O. ²Blood Group: A1 subtype. ³Brown eyes. ⁴Not European light skinned. ⁵Increased risk of baldness. ⁶Higher body mass index. ⁷Higher percentage fat mass in Caucasian and Chinese samples. ⁸Dry earwax, common in Asian people. ⁹Thick hair and Shovel shaped upper front teeth. ¹⁰More likely to have black hair (in European cohort study). ¹¹ Cold adaptation: non-synonymous change in TP53. ¹² Cold adaptation: Metabolic genes.

The ancient genome database

www.ancientgenome.dk

- Get sequence
- Compare to reference genome (NCBI 36)
- SNP accessions
- Phenotypic associations

The Saqqaq Genome Database (beta)

Enter sequence range, identifier or cheat code

Examples

Range:	17:398382..399882 (chromosome:start..end)
SNP ID:	rs17822931 or ENSSNP22423 - Ambiguously mapped SNPs and in-dels may return several records.
List phenotypic associations on chromosome:	1:phenotype

Note: Query is currently limited to 100000 records/nucleotides

The Saqqaq Genome Database (beta)

Choose alternative output format:

Result

chr	pos	ref	is_ref	genotype	pp	depth	repeat	rs	type	strand	snp_alleles
16	46815689	C	y	CC	1.6396e-13	33					
16	46815690	T	y	TT	9.9824e-14	33					
16	46815691	T	y	TT	9.995e-14	33					
16	46815692	A	y	AA	1.01e-13	33					
16	46815693	C	y	CC	3.2608e-13	32					
16	46815694	T	y	TT	1.9992e-13	32					
16	46815695	G	y	GG	6.565e-13	31					
16	46815696	G	y	GG	6.9136e-13	31					
16	46815697	C	y	CC	1.3222e-12	30					
16	46815698	C	y	CC	2.6699e-12	29					
16	46815699	C	n	TT	8.3635e-09	28		rs17822931	single	+	CT
16	46815700	G	y	GG	1.3271e-12	30					
16	46815701	A	y	AA	2.5557e-13	31					
16	46815702	G	y	GG	2.0907e-13	32					
16	46815703	T	y	TT	6.4711e-14	33					
16	46815704	A	y	AA	1.3049e-13	32					
16	46815705	C	y	CC	4.214e-13	31					
16	46815706	A	y	AA	2.5604e-13	31					
16	46815707	C	y	CC	4.4147e-13	31					
16	46815708	T	y	TT	2.5521e-13	31					
16	46815709	G	y	GG	2.1138e-13	32					

Columns explained

chr	The chromosome
pos	Position on chromosome
ref	The reference nucleotide on leading strand in hg18
is_ref	Indicates whether the genotype is the same as the reference nucleotide (y) or not (n)
genotype	The genotype called (on leading strand)
pp	For numerical reasons, we report (1-PP), where PP is the posterior probability of the genotype
depth	The number of reads covering the position
repeat	If the position lies in an annotated repeat, the ID is given here
rs	dbSNP rs-number
type	Type of dbSNP entry ("single", "indel" etc. - see the UCSC genome browser for details).
strand	Strand for dbSNP entry + (or 1) or - (or -1)
snp_alleles	Known SNP alleles, e.g. "AC" (or "A/G") for a SNP of type "single"

SNPedia

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Earwax

[rs17822931](#) determines wet vs dry earwax [[PMID 16444273](#)]

This can also be used to distinguish asian ancestry.

[NCBI coffeebreak](#) introduction

Category: [Is a medical condition](#)

[The DNA Ancestry Project](#) Discover Your Ancestry with DNA. Find Ethnic and Geographic Origins. [www.DNAAncestry](#)

[High throughput screening](#) Unknown mutations Detection BRCA1 & BRCA2 [www.fluigent.com/](#)

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Completely sequenced human genomes February 2010

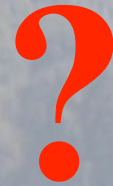
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Completely sequenced human genomes

February 2010

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Saqqaq
individual



nature

CLIMATE RESEARCH

'Next generation'
scenarios

BENZODIAZEPINES

Neural basis
to addiction

SOUTH AFRICA

Post-apartheid
science



THE ANCIENT HUMAN GENOME

Reconstructing the past from a
4,000-year-old lock of hair

NATUREJOBS
New York's
science park



From genotype to phenotype

- 99.9% of human DNA is identical to another person
- 0.1% → over 80% are single nucleotide polymorphisms (SNPs)
- The genotype of an organism is the inherited instructions within the DNA
- A phenotype is any observable characteristic or trait of an organism

Exercise: Genotype to Phenotype

<http://wiki.cbs.dtu.dk/teachingmaterials/index.php/ExGenotype2PhenotypeLite>